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Antithrombotic Medication and Incident Open-Angle Glaucoma

Michael W. Marcus,¹ Rogier P. H. M. Müskens,¹ Wishal D. Ramdas,^{2,3} Roger C. W. Wolfs,^{2,3} Paulus T. V. M. de Jong,^{2,4,5} Johannes R. Vingerling,³ Albert Hofman,² Bruno H. C. Stricker,^{2,6,7} and Nomdo M. Jansonius^{1,2}

PURPOSE. To determine the associations between the use of antithrombotic drugs and incident open-angle glaucoma (OAG).

METHODS. Ophthalmic examinations including measurements of the IOP and perimetry were performed at baseline and follow-up in 3939 participants of the prospective population-based Rotterdam Study who did not have OAG at baseline. The use of antithrombotic drugs was monitored continuously during follow-up. Antithrombotic drugs were stratified into anticoagulants and platelet aggregation inhibitors. Associations between incident OAG and the use of antithrombotic drugs were assessed using Cox regression; the model was adjusted for age, sex, baseline IOP and IOP-lowering treatment, family history of glaucoma, and myopia. Associations between antithrombotic drugs and IOP at follow-up were analyzed with multiple linear regression.

RESULTS. During a mean follow-up of 9.8 years, 108 participants (2.7%) developed OAG. The hazard ratio for anticoagulant use was 0.90 (95% confidence interval [CI], 0.55–1.48; $P = 0.69$) and for platelet aggregation inhibitors 0.80 (0.53–1.21; $P = 0.28$). There was no trend towards a reduced or increased risk

of incident OAG with prolonged anticoagulant use (P value for trend 0.84) or platelet aggregation inhibitor use (0.59). There was a significant IOP-lowering effect of anticoagulants (-0.31 mm Hg; 95% CI, -0.58 to -0.04 mm Hg; $P = 0.025$) but not of platelet aggregation inhibitors ($P = 0.06$). The IOP-lowering effect of anticoagulants disappeared after additional adjustment for the use of systemic beta-blockers.

CONCLUSIONS. Use of anticoagulants or platelet aggregation inhibitors appears not to be associated with incident OAG. (*Invest Ophthalmol Vis Sci.* 2012;53:3801–3805) DOI: 10.1167/iovs.12-9604

Open-angle glaucoma (OAG) is an insidious disease characterized by irreversible loss of retinal ganglion cells and cupping of the optic disc, ultimately resulting in loss of sight. The prevalence of OAG in the 40+ population is approximately 2%.¹ An elevated IOP is an important risk factor for OAG, and the therapeutic management of OAG is currently targeted towards the lowering of IOP. However, OAG progression often continues despite an apparently sufficient reduction of the IOP. As this IOP-independent progression is at best partially understood, more research is needed to elucidate the pathogenesis of OAG, which may result in the development of other therapeutic strategies.

Impaired blood flow has been postulated to be involved in the pathogenesis of OAG.^{2,3} Treatment with antithrombotic drugs such as anticoagulants and platelet aggregation inhibitors (PAIs) is a frequently used prophylaxis against impaired blood flow.⁴ Moreover, PAIs have been suggested to have neuroprotective properties.⁵ Some clinicians already prescribe PAIs based on the “it doesn’t hurt to try” principle. However, two recent trials in Alzheimer’s disease (like OAG, a neurodegenerative disease) showed no effect of a PAI (aspirin) on cognitive functioning, yet it increased the risk of serious bleeds.^{6,7} For all these reasons, it seems logical to study the potential role of these drugs in the management of OAG, as suggested earlier.⁸ Thus far, one study addressed the effect of PAIs (acetylsalicylic acid, ASA) on IOP,⁹ and two studies examined the effect of ASA on the progression of OAG.^{10,11} As these studies gave equivocal results (see Discussion section), another look at this issue seemed warranted. Moreover, we did not find any study addressing the effects of anticoagulants or of PAIs other than ASA on OAG.

The aim of this study was to determine the associations between the use of anticoagulants or PAIs and the development of OAG in a prospective population-based cohort study.

METHODS

Study Population

The present study was performed as part of the Rotterdam Study, a prospective population-based cohort study investigating age-related

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disorders. The study population consisted of 7983 almost exclusively Caucasians aged 55 years and older living in the Ommoord district of Rotterdam, the Netherlands.¹² For this study, data from a subset of 3939 participants who did not have OAG (see below) at baseline and who completed at least one follow-up examination were used. Differences between those who completed at least one follow-up and those who did not were published earlier.¹³ The latter were older, more often female, more often had a history of stroke, and less frequently reported a positive family history of glaucoma. The baseline examination took place from 1991 to 1993; follow-up examinations were performed from 1997 to 1999 and from 2002 to 2006. All measurements were conducted after the Medical Ethics Committee of the Erasmus University Rotterdam had approved the study protocol and all participants had given written informed consent in accordance with the Declaration of Helsinki.

Ophthalmic Assessment

Participants underwent similar eye examinations at baseline and at the two follow-up rounds. These examinations included refraction, measurement of the best-corrected visual acuity, Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland), funduscopy, fundus photography of the posterior pole, imaging of the optic disc, and visual field testing.

At each visit, three IOP measurements were taken on each eye, and the median value of these three measurements was recorded¹⁴; the higher median of both eyes was used in the analysis. The visual field of each eye was screened using a 52-point suprathereshold test that covered the central visual field with a radius of 24° (Humphrey Field Analyzer [HFA]; Carl Zeiss, Oberkochen, Germany).^{15,16} Visual field loss was defined as nonresponse to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points, or four including the blind spot. In participants with reproducible abnormalities on suprathereshold testing, Goldmann perimetry (Haag-Streit AG; baseline and first follow-up) or full-threshold HFA 24-2 testing (second follow-up) was performed on both eyes. The classification processes of the Goldmann perimetry and full-threshold HFA 24-2 test results have been described in detail before.^{13,15} In short, visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes.

Incident Open-Angle Glaucoma

We defined incident OAG as no glaucomatous visual field loss in both eyes at baseline and glaucomatous visual field loss in at least one eye at follow-up.¹³ All identified cases were examined by an experienced ophthalmologist (PTVMdJ and RCWW) who performed gonioscopy and a dilated ophthalmic exam. Cases with a history or signs of angle closure or secondary glaucoma were excluded.

Medication Data

Data on antithrombotic drugs prescriptions for all participants were obtained from seven pharmacies using a centralized computer network in the Ommoord district of Rotterdam, The Netherlands, from January 1, 1991, onward. This included the product name, Anatomical Therapeutic Chemical (ATC) code, duration of use, and the date of first prescription. Antithrombotic drugs were classified based on ATC system, according to pharmacologic subgroup, into anticoagulants (B01AA; coumarin derivatives) and PAIs (B01AC; abciximab, ASA, carbasalate calcium, clopidogrel, dipyridamole, eptifibatide, prasugrel, tirofiban). The use of antithrombotics was recorded as the number of days with use during follow-up. Usage before baseline was not taken into account.

Other Covariables

Other covariables included age, sex, smoking, diabetes mellitus, cardiovascular diseases, the use of antihypertensive drugs, the use of

statins, body mass index, total cholesterol, IOP, IOP-lowering treatment, family history of glaucoma, and myopia. All these covariables were measured at baseline. Smoking status was self-reported and categorized as “ever” or “never” smoker. Data on diabetes mellitus and cardiovascular disorders such as angina pectoris, atrial fibrillation, myocardial infarction, heart failure, hypertension, and stroke were obtained from the participants through interviews, electrocardiogram readings, and nonfasting and fasting serum blood glucose levels. Diabetes was defined as the use of antidiabetic medication or by a nonfasting or post-load plasma glucose level above 200 mg/dL (11.1 mM). Hypertension was defined as the use of antihypertensive medication for the indication of hypertension or as a systolic blood pressure of 140 mm Hg or more, or a diastolic pressure of 90 mm Hg or more. The use of antihypertensive medication and statins was determined using the pharmacy computer system as described above. Body mass and height were measured at the research center. Total serum cholesterol was measured in nonfasting blood. IOP-lowering treatment was defined as the use of IOP-lowering medication or a history of glaucoma surgery or laser trabeculoplasty. The family history of glaucoma was determined by interviews and was considered positive if the participant reported a history of glaucoma in parents, siblings, or offspring. Myopia was defined as a spherical equivalent refractive error of -4 diopters (D) and more myopia.¹⁶ Eyes with a cataract extraction before baseline were excluded from this analysis. In cases with one eye with incident OAG, the refraction of that eye was used. In participants without OAG or with OAG in both eyes, the refraction of a random eye was used.

Statistical Analysis

Differences in baseline characteristics between participants with and without incident OAG and differences in baseline characteristics between antithrombotic drug users and nonusers were evaluated using χ^2 tests for categorical variables and *t*-tests for normally distributed continuous variables. To determine the associations between the use of antithrombotic drugs and incident OAG, the use of anticoagulants or PAIs was initially defined as any use during follow-up, and the associations were initially analyzed with χ^2 tests. Subsequently, a Cox proportional hazards model was used to calculate hazard ratios (HR) and corresponding 95% CI for the associations between the use of anticoagulants or PAIs and incident OAG. Follow-up duration was used as the time axis in the model. For participants without incident OAG, the follow-up duration was counted from the baseline visit to the last visit with reliable perimetry. For incident OAG cases, the follow-up ended at the first visit in which glaucomatous visual field loss was detected. The antithrombotic drugs, age and sex, and other covariables with $P < 0.20$ in the univariable comparisons were included in the multivariate analysis. Subsequently, the antithrombotic drugs, age and sex, and other covariables with $P < 0.05$ in the initial multivariate model were included in the final model. The use of antithrombotic drugs was entered in the model as any use during follow-up. To allow for the evaluation of a possible dose-response relationship, we also performed analysis after making three nominal categories based on the duration of medication use, being no use, cumulative use during 2 years or less, and cumulative use during more than 2 years (see Discussion section). The dose-response relationship was evaluated with a trend test. To explore direct effects of the antithrombotics on the IOP, we conducted a multiple linear regression analysis, with IOP at follow-up as the dependent variable. This analysis was adjusted for IOP-lowering treatment at follow-up and for the same covariates as the final Cox model, except for baseline IOP and IOP-lowering treatment at baseline. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). A *P* value of 0.05 or less was considered statistically significant.

RESULTS

During a mean follow-up of 9.8 years, 108 participants (2.7%) developed OAG. Table 1A depicts the baseline characteristics

TABLE 1. Baseline Characteristics of Participants with and without Incident Open-Angle Glaucoma (A) and of Antithrombotic Users and Nonusers (B)*

	A			B		
	Incident Open-Angle Glaucoma (n = 108)	No Incident Open-Angle Glaucoma (n = 3831)	P Value	Antithrombotic Users (n = 1748)	Nonusers (n = 2191)	P Value
Age	68.4 (7.1)	65.7 (6.8)	<0.001	67.3 (6.9)	64.5 (6.6)	<0.001
Sex (% female)	49.1	58.7	0.046	55.0	61.1	<0.001
Smoking (%)	33.3	33.4	0.98	32.6	34.1	0.31
Diabetes mellitus (%)	8.4	6.9	0.54	9.2	5.2	<0.001
Angina pectoris (%)	1.9	3.1	0.46	4.7	1.8	<0.001
Atrial fibrillation (%)	2.8	2.1	0.63	3.8	0.8	<0.001
Myocardial infarction (%)	13.2	9.7	0.23	15.1	5.5	<0.001
Heart failure (%)	0.9	1.2	0.81	2.0	0.5	<0.001
Hypertension (%)	52.9	47.1	0.49	57.3	43.5	<0.001
Stroke (%)	2.8	1.2	0.16	2.3	0.5	<0.001
Use of antihypertensive drugs (%)	28.0	26.0	0.63	35.5	18.5	<0.001
Use of statins (%)	0.9	2.1	0.39	32.2	11.3	<0.001
Body mass index (kg/m ²)	25.8 (2.9)	26.3 (3.5)	0.12	26.6 (3.5)	26.1 (3.5)	<0.001
Total cholesterol (mM)	6.5 (1.1)	6.7 (1.2)	0.17	6.7 (1.2)	6.7 (1.2)	0.82
IOP (mm Hg)	17.3 (4.7)	15.0 (3.1)	<0.001	15.1 (3.2)	15.0 (3.2)	0.35
IOP-lowering treatment (%)	15.7	2.3	<0.001	2.5	2.8	0.47
Family history of glaucoma (%)	16.7	8.1	0.002	8.0	8.6	0.50
Myopia	9.5	4.9	0.033	5.1	5.0	0.95

* Antithrombotics include anticoagulants or platelet aggregation inhibitors, or both; data are shown with univariate comparisons (mean [SD] unless stated otherwise).

of the study population for participants with and without incident OAG. Participants who developed OAG were older and more often male, more often had a positive family history of glaucoma, and more often had myopia. They also had a higher IOP and more frequently received IOP-lowering treatment. Table 1B shows the baseline characteristics of the study population for antithrombotic drug users and nonusers.

Twenty-one of 108 (19.4%) OAG cases and 701 of 3831 (18.3%) controls ($P = 0.76$) used anticoagulants at any time during follow-up; 40 of 108 (37.0%) OAG cases and 1348 of 3831 (35.2%) controls ($P = 0.69$) used PAIs. Amongst the 722 participants using anticoagulants at any time during follow-up, the median duration of use was 231 days, with a range of 1 to 3823 days; amongst the 1388 participants using PAIs, the median duration of use was 1112 days, with a range of 7 to 4411 days.

Table 2 presents the final model, adjusting for age, sex, baseline IOP and IOP-lowering treatment, family history of glaucoma, and myopia. Participants using anticoagulants and PAIs had nonsignificant risk reductions with HRs of 0.90 and

0.80, respectively. There was no trend towards a reduced or increased risk of incident OAG with prolonged anticoagulant use (HR 0.84 [95% CI, 0.46–1.53; $P = 0.57$] for usage during 2 years or less; HR 1.04 [95% CI, 0.48–2.27; $P = 0.92$] for usage during more than 2 years; P value for trend 0.84) or PAI use (HR 0.78 [95% CI, 0.42–1.45; $P = 0.44$] for usage during 2 years or less; HR 0.81 [95% CI, 0.51–1.31; $P = 0.40$] for usage during more than 2 years; P value for trend 0.59).

Table 3 shows the results of the multiple linear regression analysis with IOP at follow-up as the dependent variable. As can be seen in this table, there was a significant IOP-lowering effect of anticoagulants and a similar but nonsignificant effect of PAIs.

DISCUSSION

This study did not demonstrate any association between the use of either anticoagulants or PAIs and incident OAG. Of interest, the use of anticoagulants seemed to be associated with a lower IOP.

TABLE 2. Final Multivariate Model of the Risk of Developing Open-Angle Glaucoma for Antithrombotic Drugs

	Hazard Ratio	95% Confidence Interval	P Value
Anticoagulants	0.90	0.55–1.48	0.69
Platelet aggregation inhibitors	0.80	0.53–1.21	0.28
Age (per year)	1.08	1.05–1.11	<0.001
Sex (female)	0.57	0.39–0.85	0.005
IOP (per mm Hg)	1.12	1.08–1.18	<0.001
IOP treatment	3.24	1.73–6.08	0.002
Family history of glaucoma	1.82	1.06–3.11	0.029
Myopia	2.09	1.08–4.04	0.028

TABLE 3. Multiple Linear Regression Analysis with Intraocular Pressure at Follow-up as the Dependent Variable

	Beta	95% Confidence Interval	P Value
Anticoagulants	−0.31	−0.58 to −0.04	0.025
Platelet aggregation inhibitors	−0.21	−0.44 to 0.008	0.06
Age (year)	−0.006	−0.021 to 0.010	0.49
Sex (female)	−0.30	−0.51 to −0.09	0.006
IOP-lowering treatment at follow-up	1.76	1.34 to 2.18	<0.001
Family history of glaucoma	0.37	−0.01 to 0.75	0.054
Myopia	0.60	0.13 to 1.08	0.012

In a retrospective cohort study performed in a clinical setting, de Castro et al. examined the effect of ASA on the optic nerve head as assessed longitudinally with confocal scanning laser ophthalmoscopy in 76 OAG suspects.¹¹ They did not find an effect of ASA use after a follow-up of 23 months, which is in agreement with our findings. Linden et al. conducted a double-blind, placebo-controlled, randomized cross-over study amongst 28 patients with ocular hypertension or OAG to determine the short-term effect of a single dose of 500 mg ASA on the IOP. There was no statistically significant difference between the placebo-treated and the ASA-treated patients.⁹ This is in agreement with our observation that the usage of PAIs was not associated with the IOP at follow-up. Bell et al. found, in a retrospective, observational, case-control study amongst 64 patients undergoing trabeculectomy and 74 controls, an association between ASA use and an increased frequency of glaucoma surgery, suggesting a harmful effect.¹⁰ The major limitation of their study, as reiterated by the authors, was that they equated the frequency of glaucoma surgery with the progression of glaucoma. This assumption might have biased the effect estimate. Although they found a significant harmful effect, whereas we did not, the 95% CI for ASA use in their study (1.10–4.79) overlaps with our 95% CI for PAI use (0.53–1.21).

Although we did not find a significant beneficial or harmful effect of anticoagulants or PAIs on the incidence of OAG, there was a significant IOP-lowering effect of anticoagulants. Of interest, the anticoagulant heparin has been associated with an increased outflow facility in human and monkey trabecular meshwork,^{17–19} providing at least a glimpse of a possible biological explanation for this unexpected finding. Although our finding may thus support a hypothesis regarding IOP regulation, the clinical significance is at most modest, as the R^2 was only 0.03 (i.e., the percentage of the IOP at follow-up, explained by the anticoagulant use in the regression model, was 3%), and the effect estimate was only approximately -0.3 (i.e., those using anticoagulants had—on average—a 0.3 mm Hg lower IOP than those not using anticoagulants). The combination of a significant IOP-lowering effect and no effect on the incidence of OAG might point to a harmful IOP-independent effect of anticoagulants on OAG. However, with a 12% increase in OAG risk per millimeter Hg increase in IOP (Table 2), the effect of a 0.3 mm Hg lowering of the IOP is amply within the 95% CI as reported in Table 2. Apart from a possible biological mechanism explaining the IOP-lowering effect of anticoagulants, confounding by, for example, the use of systemic beta-blockers at follow-up could have occurred. If we adjusted the analysis as presented in Table 3 for beta-blocker use at follow-up, the IOP-lowering effect of anticoagulants was no longer significant (effect estimate -0.031 mm Hg; $P = 0.78$).

In an earlier study, we reported that the use of statins was associated with a reduced risk of OAG.²⁰ Therefore, the use of statins may be regarded as a confounding factor in the present study. In the present study, we corrected—in accordance with the assumptions of the Cox model—for the use of statins at baseline. As the use of statins increases rapidly with age, we explored adjusting for statin use during follow-up as well. No changes were observed in the HRs of either the anticoagulants or the PAIs. In another study, we reported that a higher body mass index was associated with a reduced risk of OAG. No other lifestyle/socioeconomic factors were associated with OAG.²¹ Body mass index appeared not to be a confounding factor in the current study.

Strengths of our study include its prospective and population-based design, the large number of participants, and the long follow-up period. Information bias was prevented by prospectively and completely automated collection of

pharmacy records of all prescriptions. Although this approach guarantees accurate prescription data, especially because at every data download, missing participants were traced,¹² a complete overview of medication prescriptions does not guarantee that all participants actually took their medication. In this respect, it is important to mention that the monitoring of the users of anticoagulants is well organized in The Netherlands (by means of regular blood sampling and the provision of personalized dosing schemes). Also, especially the PAIs that irreversibly block the platelet aggregation (like ASA) have a long therapeutic half-life (approximately 10 days; determined by the physiological turnover of platelets). This should make the effect of these drugs resistant against an irregular intake. Nevertheless, noncompliance may have resulted in a too conservative risk estimate, inhibiting the discovery of small, harmful or protective effects. The usage of antithrombotics before baseline was not taken into account. This is an intrinsic limitation of the Rotterdam Study because the onset of the automated collection of medication data started at baseline, which may have caused an underestimation of potential harmful effects. The reason for this bias is that our outcome measure was incident OAG, which implies that we excluded participants who had OAG already at baseline (possibly related to harmful effects of antithrombotics used before baseline). To explore this potential bias, we repeated the analysis presented in Table 2 after the exclusion of subjects already using antithrombotics at baseline. Thirteen of 108 cases and 159 of 3831 controls were excluded. The resulting HRs were 0.77 (0.43–1.37) for anticoagulants and 0.71 (0.45–1.11) for PAIs. This suggests that this bias can be ignored.

A possible limitation of this study is potential misclassification of exposure. This misclassification will be random because the outcome is, inextricably, gathered irrespective of exposure status. To appreciate this approach, it is important to realize that OAG development often takes more than a decade and that OAG cannot be detected in the earliest stages. This implies that some incident OAG cases may already have had preperimetric changes at baseline,¹³ whereas some controls may actually have had preperimetric changes at follow-up. Some factors slow down or accelerate the disease development and thus make it less likely or more likely that the disease has reached a certain stage at a certain point in time (being our follow-up examination) given that this stage was not yet reached at baseline. Cumulative exposure stratified into biologically plausible nominal categories as we used in our analyses is the best proxy for studying the overall influence of the use of medication on the rate of glaucoma development during follow-up.²² Because the exposure misclassification is random, it will tend to bias the results towards the null hypothesis. This might have hampered the detection of small effects in our study.

Another factor that might have hampered the detection of small effects is the limited number of OAG cases. This is a limitation of the population-based design. The size of our study population was determined by the original design of the Rotterdam Study. The power of the Rotterdam Study was directed towards common diseases in the elderly, which tend to have higher prevalences than OAG—despite the fact that OAG is a very common eye disease. However, once an analysis has been finished, the confidence intervals of the effect estimates tell the whole story, and this implies that small protective or harmful effects could have been overlooked in our study. However, larger effects, if they would exist, would have been detected.

In conclusion, to the best of our knowledge, this is the first study examining the effects of the use of anticoagulants on OAG, and the first population-based study examining the effects of PAIs on OAG. We found no clear associations. As

anticoagulants and PAIs are commonly prescribed in the elderly, this finding has clinical implications. Our study does not support withdrawing these drugs, if prescribed for cardiovascular disease, in patients with OAG. Similarly, our study does not support the use of these drugs as part of the treatment of OAG.

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